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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE	Application Number	09/632,735
	Filing Date	August 4, 2000
	First Named Inventor	BAEZA-RAMIREZ
	Group Art Unit	1641
	Examiner Name	K. Padmanabhan
	Attorney Docket Number	2480-103
Title: METHODS FOR DIAGNOSTIC AND/OR TREATMENT OF ANTIPHOSPHOLIPIDS ANTIBODIES-RELATED DISEASES AND DEVICES		

DECLARATION UNDER RULE 132

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Maria Isabel Baeza-Ramirez, Ph.D., declare as follows:

1. I am the same Maria Isabel Baeza-Ramirez named as the co-inventor of the above-identified patent application. A copy of my C.V. is attached as Exhibit A.

2. The present invention concerns a diagnostic method of indirectly determining the presence of lipidic particles in cell membranes from a sample suspected of having anti-lipidic particle antibodies from an individual suspected of suffering primary antiphospholipid syndrome or a disease associated with secondary antiphospholipid syndrome. In addition, the present invention is directed to a kit for such diagnosis. The diagnostic method makes use of anti-lipidic particle antibodies as described in the specification.

3. I have read and understand the Office Action issued by the U.S. Patent and Trademark Office on January 27, 2003.

Exhibit 1

4. Claims 32, 35-38, 46, 48, 52-59, 91-92 and 94 of the application have been rejected under 35 U.S.C. § 102(b) as anticipated by Loizou et al (Clin. Exp. Immunol., 1985). In addition, claims 32, 35-38, 46, 52-59, and 91-95 of the application have been rejected under 35 U.S.C. § 102(b) as anticipated by, U.S. Patent 5,840,587, issued to Stewart et al. Neither Loizou et al nor Stewart et al disclose or suggest the anti-lipidic particle antibodies in my claimed invention.

5. Cardiolipin and other phospholipids are structurally organized in liposomes or hexagonal II arrangements which are different from lipidic particles. Cardiolipin is a phospholipid, which is associated in closed phospholipid bilayers or liposomes when found in an aqueous media (Page 4, lines 22-25) (Exhibit B, Figure A). However, cardiolipin in the presence of divalent cations changes its molecular association in said aqueous media and forms hexagonal II arrangements (Page 4, lines 28-30) where cardiolipin is associated in a tubular form (Exhibit B, Figure B). Additionally, when cardiolipin is forming liposomes together with other phospholipids such as phosphatidylcholine, and those liposomes are treated with divalent cations or drugs that produce lupus induced by drugs in human beings the formation of a different and special phospholipid arrangement (called lipidic particle) occurs (Page 5, lines 6-13; page 12, lines 30-34 and page 13, lines 1-3). This special phospholipid molecular arrangement is schematically shown in Figure C (Exhibit B). Therefore, anti-cardiolipin antibodies as are disclosed in Loizou et al and Stewart et al are of a particular type different than those in the present invention.

6. Cardiolipin and phospholipids can be induced, under special circumstances, to form an unique structural arrangement namely, lipidic particles. Lipidic

particles are defined on page 5, lines 1-5 of the specification as "lipidic arrangements in hexagonal or micellar phases, as well as any other structural arrangement of lipids that does not form a bilayer but that is immersed in a bilayer". Additionally, "lipidic particles are formed by incubation of liposomes with an effective amount of the lipidic particle inductor agent (divalent cations: Ca or Mn, or drugs that produce lupus induced by drugs in human beings such as chlorpromazine or procainamide) at a temperature between 25 to 40°C" (Page 13, line 34 to page 14, line 7). Thus the structure of these lipidic particles immersed in a biological bilayer (a cell membrane) is very different from the structure of a cardiolipin bilayer or a hexagonal II arrangement of cardiolipin. The present invention is directed to anti-lipidic particle antibodies.

7. The antibodies in the present invention are anti-lipidic particle antibodies and not anti-cardiolipin or anti-phospholipid antibodies. Anti-lipidic particle antibodies are not directed to an individual type of phospholipid but recognize a lipidic particle structure containing multiple different phospholipids. Phospholipids such as cardiolipin associated in lipidic particles in the lipid bilayers of liposomes or cells are the antigens used in this specification. In consequence, the monoclonal antibodies used in the present invention specifically react with phospholipids associated in lipidic particles in liposomes or in cells, and they do not react with phospholipids associated in other molecular arrangements, such as liposomes or hexagonal II arrangements. In a similar way the polyclonal antibodies detected in the present invention are antibodies against phospholipids associated in lipidic particles in liposomes or in cells (Exhibit B, Figure C). The antigens used in the present invention are therefore very different from the antigens as used in Loizou et al and Stewart et al. In Stewart et al. polystyrene microspheres suspended in absolute ethanol (Col. 8, lines 24-25 and 50-54 of Stewart et al) are coated with

cardiolipin dissolved in ethanol (Exhibit B, Figure E), while in Loizou et al. cardiolipin dissolved in ethanol is bound to ELISA polystyrene plates (Page 739, lines 46-48 of Loizou et al.) (Exhibit B, Figure D). It is clear indeed that in both methodologies there are no phospholipid bilayers nor any inductors for the formation of lipidic particles. In consequence the antigens used by Stewart et al. and by Loizou et al. are completely different from the antigens used in the present invention. Then, it is also clear indeed that the antibodies that identify phospholipids bound to solid surfaces are completely different from the antibodies that identify phospholipids forming lipidic particles in liposomes or in cells as described in the specification of the present invention. Therefore, the anti-lipidic particle antibodies of the present invention are those antibodies that recognize the phospholipids in a particular structural environment different from the liposomes or hexagonal II arrangements. In contrast, the antibodies according to Loizou et al. and Stewart et al. are different as these recognize phospholipids such as cardiolipin bound always to a solid phase.

8. Claims 32, 35-38, 46, 48-49, 53-55, 59, and 91-95 of the application have been rejected under 35 U.S.C. § 103(a) as obvious over Ramirez et al (Instituto Politecnico Nacional, 1994 or 1997) in view of Sugi et al (Blood, 1995). In the present invention the presence of anti-lipidic particle antibodies in a sample from an individual is correlated with the first stages of primary antiphospholipid syndrome or a disease associated with secondary antiphospholipid syndrome. The Ramirez et al disclosures, although describing the anti-lipidic particle antibodies does not teach or suggest this correlation between the detection of the antibodies and the first stages of an illness in a human. A person having ordinary skill in the art at the time of the invention could not have predicted the detection of the anti-lipidic particle

antibodies to be associated with the early stages of either primary antiphospholipid syndrome or a disease associated with secondary antiphospholipid syndrome, based on the prior art.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

April 14, 2003

Date

Maria Isabel Baeza-Ramirez, Ph.D